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- I have no relevant financial relationships with the manufacture of any commercial products and/or providers of commercial products discussed in this presentation.
- I do not intend to discuss unapproved investigative use of a commercial product/device in my presentation....but nothing is approved in children. I will discuss the use of aspirin and heparin and endovascular devices without reference to trade names or specific brands, formulations, or products.
- My wife was given 10 shares of Starbucks by her father. I will try and keep you awake, but perhaps you would enjoy a refreshing caffeinated beverage......

Required Disclosure Slide

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 - I. register for the event,
 - > 2. attend the entire session, and
 - 3. complete evaluation before leaving the conference.

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I will discuss off label use of aspirin and heparin and endovascular devices in children as nothing is approved in children

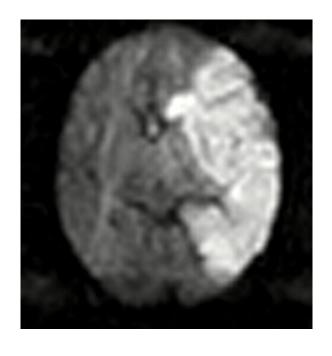
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Impact of Pediatric Stroke

- As common as brain tumors or leukemia
- One of the top causes of death
 - Age I-4 Ranked IIth
 - Age 5-9 Ranked 10th
 - Age 10-14 Ranked 8th
 - Age 15-19 Ranked 10th
- Incidence 3-15/100,000/year



 As common as childhood cancers, yet limited clinical guidelines and systematic research and no randomized clinical trials for intervention or prevention



Incidence of Stroke is Increasing

- Increased awareness and reporting
- Improvement in radiographic diagnosis

Increasing survival in previously lethal diseases that

predispose to stroke

- Congenital heart disease
- Leukemia
- Prematurity
- Sickle Cell Disease



Different Strokes in Little Folks

- Presentation in children is more subtle
 - Wide differential diagnosis
 - Seizures and Headaches are more prevalent
- Risk Factors are different from adults
 - Risk factors are multiple, age-related, and poorly understood
 - Congenital heart disease, coagulopathies, vascular abnormalities in children
 - Adult RFs; atherosclerosis, A-fib, HTN, DM are rare
 - Adults have targeted approach to prevention and treatment
- Coagulation, vascular, and neurological systems differ



Different Strokes in Little Folks

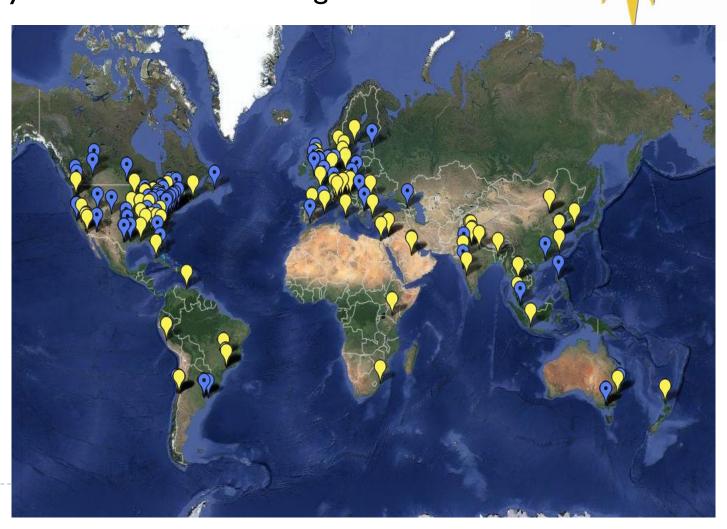
- Cannot predict or prevent with lifestyle changes
- No "established" treatments in children
- New Measures
 - PedNIH Stroke Scale
 - PSOM: Pediatric Stroke Outcome Measure
 - ▶ RRQ: Recovery and Recurrence Questionnaire
 - Classification: TOAST is toast...CASCADE
 - ► Childhood AIS Standardized Classification And Diagnostic Evaluation
- Better Outcomes

International Pediatric Stroke Study

Started January 2003

302 investigators

- 199 centers(75 enrolling)
- ▶ 45 countries
- As of 2015 Data lock
 - ▶ n= 4267
 - ▶ UTSW= 225



Are We There Yet? What to "Measure"

- Are we recognizing stroke in children in the ER?
 - Screening Tools
- How much evidence is in our "Evidence Based Guidelines"?
- What is an adequate/complete diagnostic evaluation?
- Are we "ready" for Performance Measures?
- How effectively are we treating?
- Short-term outcome measures
- Long-term clinical outcomes



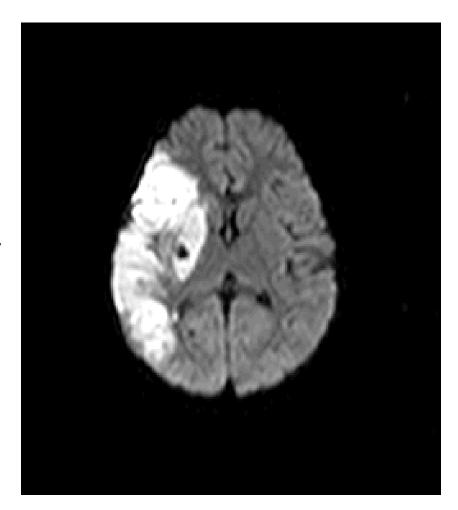
Are We There Yet? Stroke Recognition

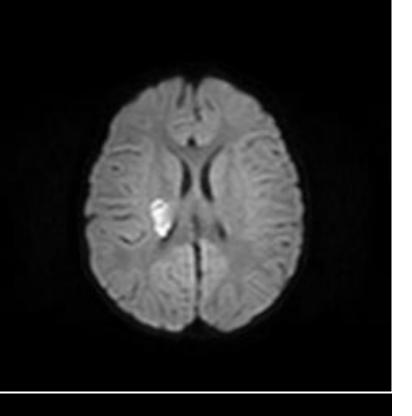
- ▶ 3 yo boy with history of complex congenital heart disease
 - Single ventricle physiology
 - ▶ I month s/p palliative surgery with fenestrated Fontan
- Fell to the floor while playing and could not move left arm or leg and he was drooling from the left side of his mouth
- Taken to outside hospital
 - Radiographs of left arm and leg were normal
 - Discharged home with splint
- ▶ 8 hours later mother brought him to CMC ERC

Are We There Yet? Stroke Recognition

MRI showed R MCA infarct

- MRA with absence of flow in R MI segment of MCA
- Cardiac MRI showed thrombus in the Fontan pathway







5 More Cases Like This

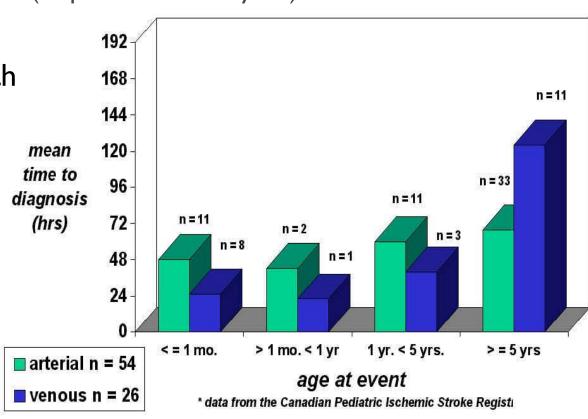


We're not there yet.....

Missing the Diagnosis

- > 60 % of children with acute stroke: diagnosis is delayed
 - > 12 hours after onset (to adult tertiary ER)
 - > 24 hours after onset (to pediatric tertiary ER)

I 0% of children with AIS have had a "missed" prior stroke or TIA





Points

- Education of Physicians/Nurses/EMT
 - Stroke Recognition
- Education of Parents of High Risk Groups
 - Stroke Recognition
 - Stroke Medic-Alert in
 - ▶ High Risk Cardiac Patients?
 - ▶ SCD?
 - Moyamoya?



Screening Tools

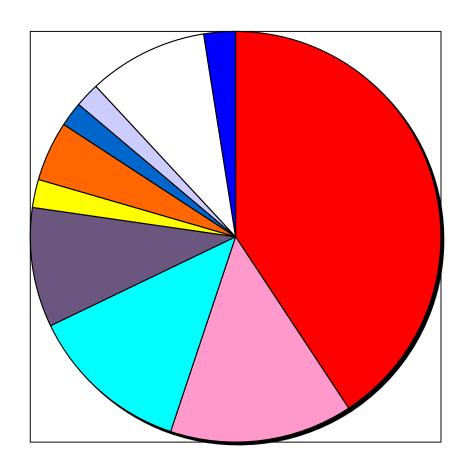
- In adults, multiple screening tools predict presence of stroke with reasonable sensitivity and specificity
- They don't work in children
 - Case/Control Study of an adult stroke tool in childhood AIS
 - COTS (Central Ohio Trauma System) screening tool
 - □ Dec LOC, slurred speech, facial droop, arm drift
 - ▶ 58 children with AIS
 - ▶ 57 Controls with Bells palsy or acute hemiparesis
 - COTS stroke scale was NOT DIFFERENT between AIS and controls

Screening Tools

- In adults, multiple screening tools predict presence of stroke with reasonable sensitivity and specificity
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 - Case/Control Study of an adult stroke tool in childhood AIS
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 - ▶ 58 children with AIS
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 - COTS stroke scale was NOT DIFFERENT between AIS and controls
- But, what do we want to measure with the scale?
 - Stroke or need for a stat MRI?

CMC Acute Stroke Team 5 Year Summary

361 AST calls/334 pts



- Stroke (41%)
- TIA (14%)
- **■** Seizure (13%)
- Migraine (9%)
- □ Conversion (2%)
- Meth/PRES (5%)
- **■** Trauma (2%)
- Tumor (2%)
- □ Other (9%)
- Unknown (2%)

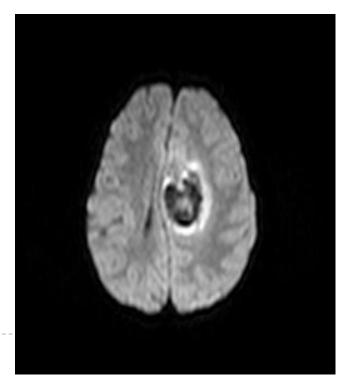
Screening Tools

- With a high prevalence of stroke mimics in children what do we want the screening tool to measure?
 - Stroke?
 - "Actionable MRI finding"?

We may want to measure "need" for that urgent MRI at

2:00AM

- ADEM
- PRES/methotrexate
- Tumors
- Trauma
- Neuroradiology happy with our false alarm rate



Points

- ▶ Education of Physicians/Nurses/EMT/High Risk Groups
- Screening Tools to Screen for what?
 - Stroke?
 - Pretty good reason to get stat MRI?





Published Guidelines

American Heart Association

Roach, et al., Management of Stroke in Infants and Children. Stroke. 2008; 39: 2644-2691.

American College of Chest Physicians

Monagle, et al., Antithrombotic Therapy in Neonates and Children. Chest. 2012; 141(2)(Suppl): e737S-e801S

Guidelines Are the Experts there yet?

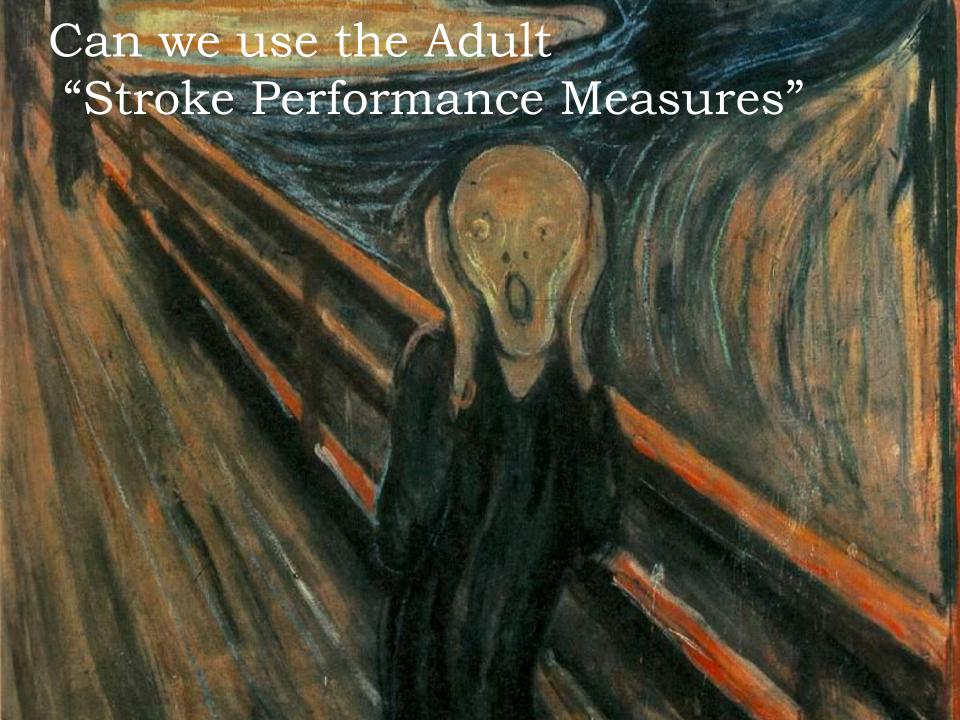
How good are the guidelines?

- Roach Stroke Guidelines: Of 93 recommendations
 - Only 2 graded level of evidence "A"
 - ▶ Transfusion for children with SCD and abnormal TCD
 - ▶ Provide factor replacement for children with factor deficiency
 - ▶ 17 are "level B" evidence from single or non-randomized trials
 - Rest are "level C" from expert opinion, case studies or standard of care

Points

- ▶ Education of Physicians/Nurses/EMT/High risk patients
- Screening Tools to Screen for what?
- Evidence Based Guidelines need Evidence



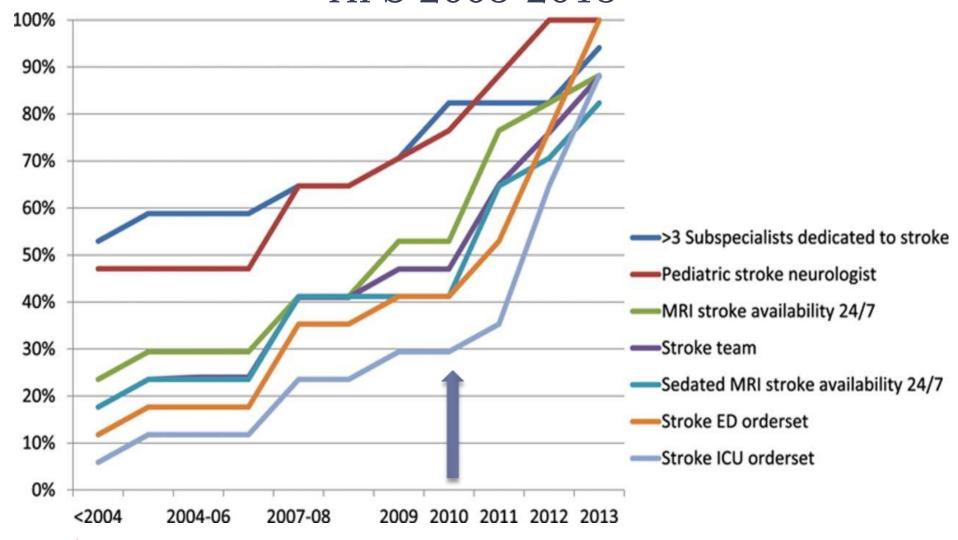


AHA/ASA Performance Measures for AIS

- Venous thromboembolism prophylaxis ?
- Discharged on antithrombotic therapy
- Anticoagulation therapy for atrial fibrillation/flutter ?
- Thrombolytic therapy ???
- Antithrombotic therapy by end of hospital day 2?
- Discharged on statin medication ???
- Stroke education
- Tobacco use counseling ???
- Assessed for rehabilitation
- Time to intravenous thrombolytic therapy ???
- Dysphagia screen: assessment
- Dysphagia screen: management
- NIHSS assessment
- Cardiac monitoring ???
- Early carotid imaging ???

These measures specifically exclude patients < 18 years old!

Development of Pediatric Stroke Centers: TIPS 2003-2013





Points

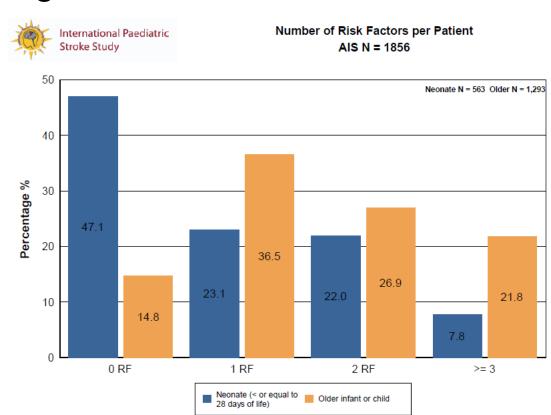
- ▶ Education of Physicians/Nurses/EMT/High risk patients
- Screening Tools to Screen for what?
- ▶ Evidence Based Guidelines need Evidence
- Its time for some **Pediatric** Stroke Performance Measures





Stroke Evaluation: Do we have to do everything?

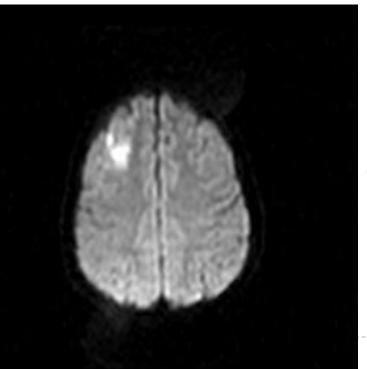
- ▶ In the IPSS, even without systematic evaluation 50% had 2 or more risk factors
- Does childhood AIS represent a "perfect storm" with multiple RFs contributing to stroke?
 - Does every patient need every test?
 - Full hypercoag eval?
 - Echocardiogram?
 - Vascular Imaging?
- What about SCD?



Oliver

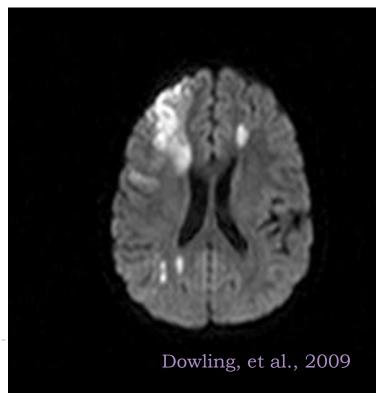
11 y.o. with Hgb SS presented with severe HA following transfusion for aplastic crisis. Severe HA recurred on Day 3 Neuro Examination normal.

No vasculopathy



PFO identified

Elevated α-phospholipid Ab Lipoprotein a Factor VIII



Potential R-to-L Shunting in SCD patients with Stroke vs Controls

	SCD/Stroke (n=153)	Control (n=129)	р
Shunting Detected	43.1%	20.0%	<0.001

- Increased prevalence of potential right-to-left shunting in SCD/stroke patients compared to non-SCD non-stroke controls
- Contrasted echocardiogram
- Any Intracardiac or Intrapulmonary shunting ("late bubbles")





Points

- ▶ Education of Physicians/Nurses/EMT/High risk patients
- Screening Tools to Screen for what?
- ▶ Evidence Based Guidelines need Evidence
- Need Pediatric Stroke Performance Measures
- Everybody may need Everything Evaluated
 - Or maybe everybody might need MORE
 - Multiplicity of RF... "perfect storm"





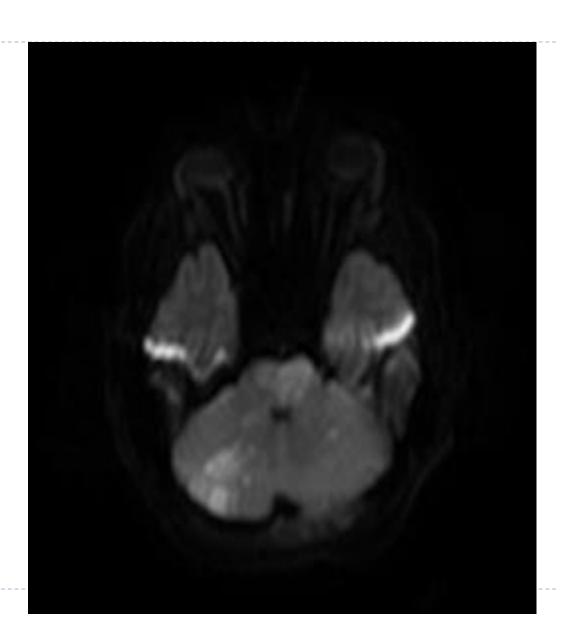
LEFT LICA AP

(Filt. 5)

Seq: 1 FRAME = 19 / 25 MASK = 1 Li Li Pk

Case

- ▶ 16 yo M
- Wrestling
- Unsteady
- Unable to walk



Vertebral and basilar arteries absent

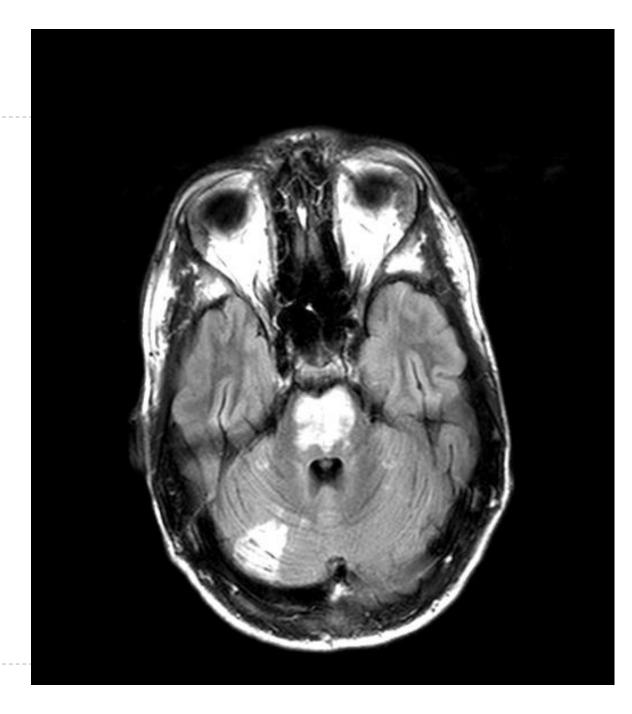


- After tPA and clot extraction
- Reconstitution of posterior circulation



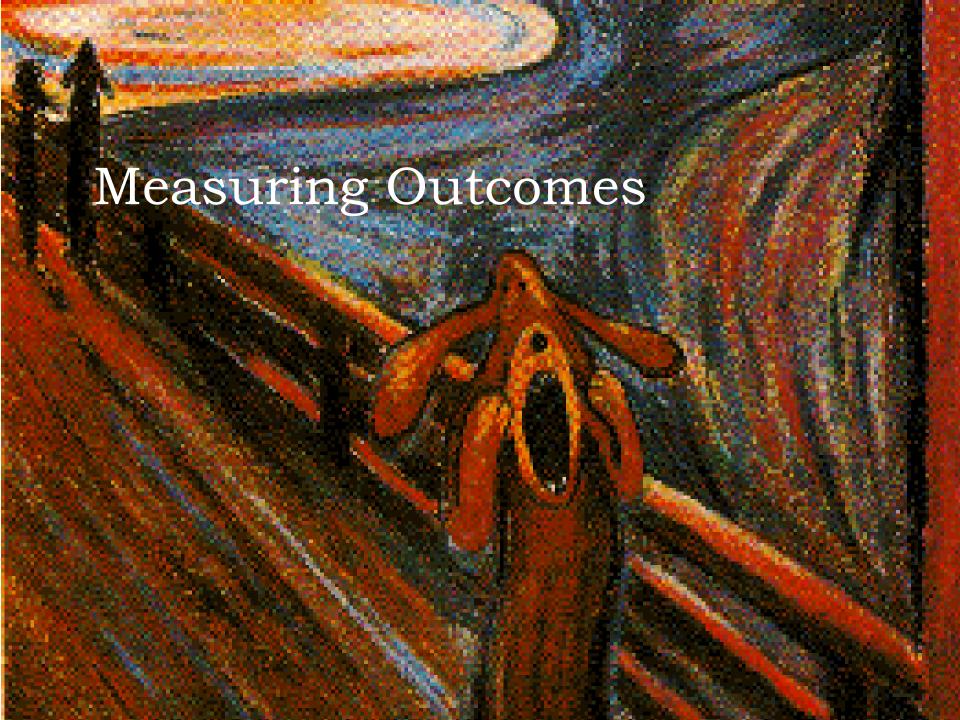
▶ Pontine infarct

Locked-in syndrome





Posterior circulation stroke survival and outcomes are better in children than adults in several series



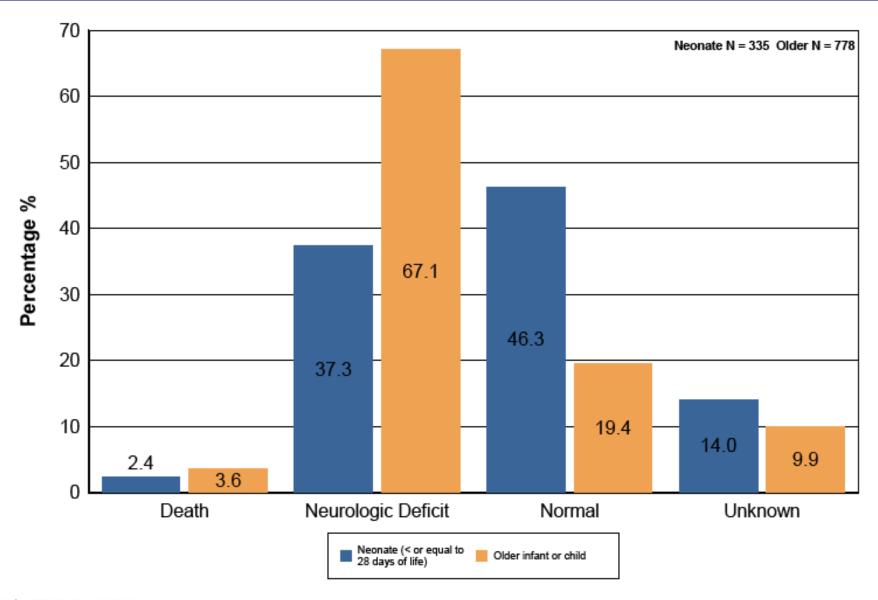
Outcomes in Pediatric Stroke Trials

- Death
 - Easy but hopefully rare
- Bleed/hemorrhagic transformation
- Recurrence
 - Silent/overt/extension
 - Early/late
- ▶ Clinical Outcome measures: Motor, sensory, language, cognitive
- Functional abilities
- Long term outcomes
- QOL: Quality of life
- Safety?
- Cost?





Neurological Status at Discharge - AIS N = 1113

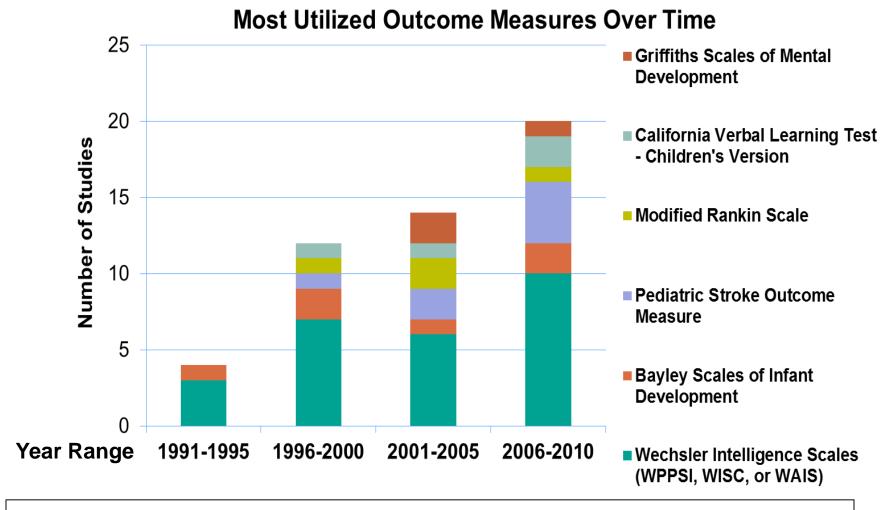


Short Term Outcomes

- ▶ How important is early recurrence or extension?
 - > 27/54 (50%) of patients with AIS had infarct recurrence or extension on routine f/u MRI at <2w
 - Most were clinically silent or difficult to determine in children
 - Per CMC protocol, all pts w/o contraindication are Rx with heparin
- Can early recurrence/extension on MRI be used as early outcome measure for trials?
- Do we need more intense treatment?
 - ASA plus Heparin if 50% are having early recurrence or extension?



Outcome Measures in Pedi Stroke Studies



Huge variety of measures used! **38 measures used in 34 Studies**. Mean 2 measures per study. Study outcomes not comparable....



Standard Pediatric Outcome Measures

- Pediatric Stroke Outcome Measure
 - The <u>only</u> validated outcome measure in pediatric stroke
- Standardized Neuro Exam
- Range: 0 to 10; <u>0 is best</u>

- Each subscore assigned:
 - 0 (no deficit)
 - ▶ 0.5 (mild/no impact on fxn)
 - 1 (moderate w some limited fxn)
 - 2 (severe/profound)

- PSOM = 5 subscores:
 - Sensorimotor right
 - Sensorimotor left
 - Language Deficit Production
 - Language Deficit -Comprehension
 - Cognition/Behavior

- Many other measures utilized:
 - Developmental Scales
 - Intelligence tests
 - Pediatric Evaluation of Disability Inventory ("Ped Barthel")
 - mRS
 - KOSCHI



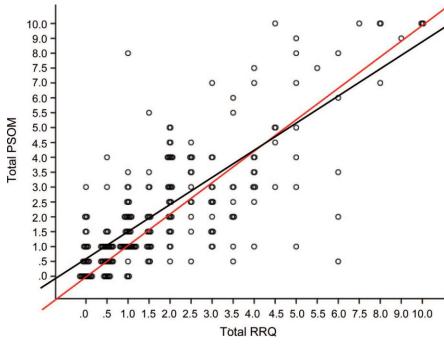
Outcome Measure Challenges

- Children grow and develop
 - Stroke can change developmental trajectory
- We need outcomes from when children are no longer under our care
 - College?
 - Employment?
 - Family?
 - Will this child be able to live independently?
- Preexisting Deficits in our high risk AIS population
 - Congenital heart disease
 - Cancer
 - Genetic syndromes (Downs)



What if they don't come back?

- Recurrence and Recovery Questionnaire (RRQ)
 - PSOM converted for telephone interview
 - Validated in a cohort of 232 children with AIS or CSVT and same day neurologist performed PSOM and parents RRQ responses
 - RRQ was a reliable estimator of PSOM total & components
 - Chronic illness effect: increased difference between total PSOM and RRQ scores.
 - RRQ can be used when child cannot return for examination in long-term follow up studies



Problem

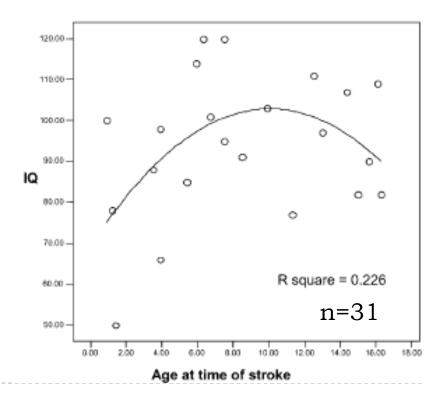
- What's a good outcome?
 - PSOM ≥ I = poor outcome?
 - Does it depend on your starting point?
 - Locked in patient, recovers to PSOM =2
 - ▶ I for motor R, 0.5 motor left, 0.5 behavioral
 - ▶ This would be classified as poor outcome
 - Berlin Heart Study used different criteria (as alternative to use of this ventricular assist device was death)
 - Unacceptable neurologic deficits
 - Comatose
 - □ Quadriplegia (PSOM 3-4 on motor scale)
 - □ Severe Global Aphasia (PSOM 3-4 or language scales)
 - □ Severe Cognitive deficits (PSOM 2 on cognitive scale)
- All scales are imperfect, but need careful analysis with analysis of subcomponents
- Mostly, we need data

Tantalizing Observations from Single Center Studies

- Early or "selective vulnerability" at early ages
- Localization cortical/subcortical effects as well

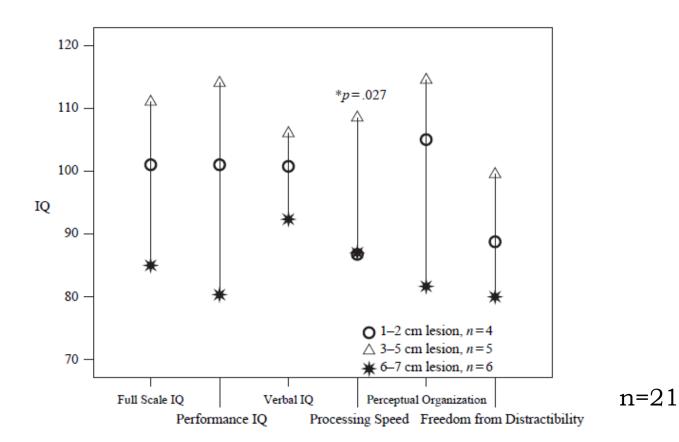
Index measure	Perinatal	1mo-5y	6-16y	F	p
FSIQ*	91.63 (14.30)	95.42 (15.65)	97.21 (13.51)	2.88	0.0
/IQ/VCI	92.20 (14.17)	97.60 (15.20)	97.98 (13.04)	2.09	0.0
PIQ/PRI	94.33 (13.31)	96.37 (14.62)	99.00 (15.62)	1.90	0.1
MMI	88.10 (16.00)	93.98 (14.92)	97.40 (13.67)	4.95	0.0
	89.63 (14.44)	93.31 (12.56)	93.17 (14.89)	0.53	0.5



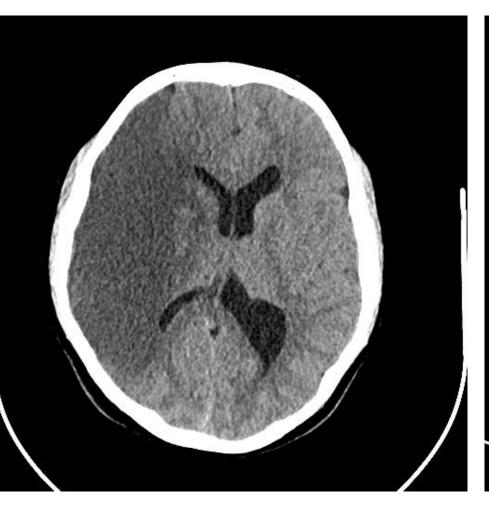


Tantalizing Observations from Single Center Studies

Lesion size might be important



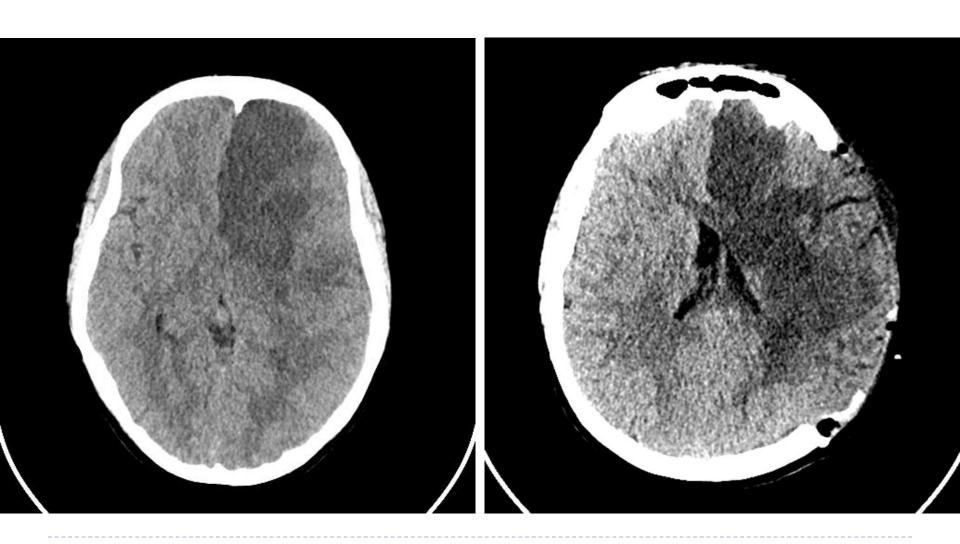
Case A Decompressive Hemicraniectomy CT 1/2015





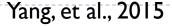


Case B Decompressive Hemicraniectomy CT 6/2015



Meta-analysis of DH RCTs in ADULTS

- 6 Randomized controlled studies of DH for malignant MCA stroke (314 patients total) with Primary outcomes;
 - Death
 - Disability by Modified Rankin Score
 - ► Major disability >3
 - Severe disability >4
 - \triangleright mRS 0 = No symptoms
 - ▶ mRS I = No significant disability. All usual activities ok
 - mRS 2= Slight disability...able to look after own affairs but can't do all prior activities
 - mRS 3 = moderate disability, able to walk unassisted, requires some help
 - mRS 4 = moderately severe disability, unable to attend to own bodily needs without assistance and unable to walk unassisted
 - mRS 5 = Severe, requires constant nursing case and attention, bedridden, incontinent
 - ▶ mRS 6= Dead





Meta-analysis of DH RCTs Death at 12m

A								
	DHC	;	Contr	ol		Peto Odds Ratio		Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Year	Peto, Fixed, 95% CI
5.1.1 Age ≤ 60 years	i							
DESTINY 2007	3	17	8	15	9.9%	0.22 [0.05, 0.91]	2007	-
DECIMAL 2007	5	20	14	18	13.0%	0.13 [0.04, 0.45]	2007	
HAMLET 2009	7	32	19	32	20.9%	0.22 [0.08, 0.58]	2009	
Zhao 2012	1	8	7	10	6.2%	0.11 [0.02, 0.68]	2012	
Subtotal (95% CI)		77		75	50.0%	0.17 [0.09, 0.33]		•
Total events	16		48					
Heterogeneity: Chi2 = 0	0.74, df = 3	3(P=0)	0.86); I ² =	0%				
Test for overall effect:	Z = 5.36 (I	P < 0.0	0001)					
5.1.2 Age > 60 years								
Zhao 2012	3	16	9	13	9.6%	0.13 [0.03, 0.58]	2012	
DESTINY II 2014	20	47	47	62	34.1%	0.25 [0.11, 0.54]	2014	<u> </u>
Subtotal (95% CI)		63		75	43.7%	0.22 [0.11, 0.43]		•
Total events	23		56					
Heterogeneity: Chi ² = 0	0.54, df =	1 (P = ().46); I ² =	0%				
Test for overall effect:	Z = 4.37 (1	P < 0.0	001)					
5.1.3 Unclear								
Slazins 2012	6	11	12	13	6.2%	0.15 [0.02, 0.89]	2012	
Subtotal (95% CI)		11		13	6.2%	0.15 [0.02, 0.89]		
Total events	6		12					
Heterogeneity: Not app	plicable							
Test for overall effect:	Z = 2.08 (1	P = 0.0	4)					
Total (95% CI)		151		163	100.0%	0.19 [0.12, 0.30]		•
Total events	45		116					
Heterogeneity: Chi ² =	1.58, df =	6 (P = 0	0.95); I ² =	0%				0.01 0.1 1 10 100
Test for overall effect:	Z = 7.20 (1	P < 0.0	0001)					Favours DHC Favours Control
Test for subaroup diffe	rences: C	$hi^2 = 0.$	31. df = 2	(P = 0)	.86). $I^2 = 0$	%		Tavoura Di 10 Tavoura Contion

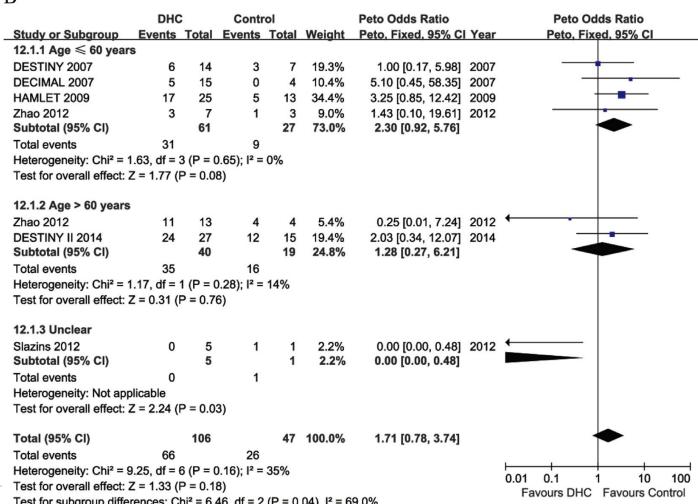
Meta-analysis of DH RCTs: Death or Severe Disability at 12m (mRS>4)

В								
Б	DHC		Contr	ol		Peto Odds Ratio		Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Year	Peto, Fixed, 95% CI
4.1.1 Age ≤ 60 years								
DECIMAL 2007	5	20	14	18	14.9%	0.13 [0.04, 0.45]	2007	
DESTINY 2007	4	17	10	15	12.4%	0.18 [0.05, 0.73]	2007	
HAMLET 2009	13	32	19	32	24.9%	0.48 [0.18, 1.26]	2009	
Zhao 2012	1	8	7	10	7.1%	0.11 [0.02, 0.68]	2012	
Subtotal (95% CI)		77		75	59.3%	0.24 [0.13, 0.44]		•
Total events	23		50					
Heterogeneity: Chi ² = 3	3.73, df = 3	3(P=0)).29); I ² =	20%				
Test for overall effect: 2	Z = 4.50 (I	P < 0.0	0001)					
4.1.2 Age > 60 years								
Zhao 2012	5	16	13	13	10.7%	0.06 [0.01, 0.26]	2012	
DESTINY II 2014	29	47	62	62	22.8%	0.06 [0.02, 0.18]		
Subtotal (95% CI)		63		75	33.5%	0.06 [0.03, 0.14]		•
Total events	34		75					
Heterogeneity: Chi2 = 0	0.01, df =	1 (P = ().94); l ² =	0%				
Test for overall effect: 2	Z = 6.49 (o.0 > c	0001)					
4.1.3 Unclear								
Slazins 2012	6	11	12	13	7.1%	0.15 [0.02, 0.89]	2012	
Subtotal (95% CI)	Ū	11		13	7.1%	0.15 [0.02, 0.89]		
Total events	6		12					
Heterogeneity: Not app	olicable							
Test for overall effect: 2		P = 0.0	4)					
Total (95% CI)		151		163	100.0%	0.15 [0.09, 0.24]		•
Total events	63		137					
Heterogeneity: Chi ² = 9	9.90, df =	6 (P = 0).13); I² =	39%				0.01 0.1 1 10 100
Test for overall effect: 2	Z = 7.78 (o.0 > c	0001)					Favours DHC Favours Control
 Test for subaroup diffe 	rences: C	$hi^2 = 6.$	17. df = 2	(P = 0.	05). $I^2 = 6$	7.6%		Tatodia Di lo Tatodia Collidi



Meta-analysis of DH RCTs Major Disability in survivors (mRS 4-5)

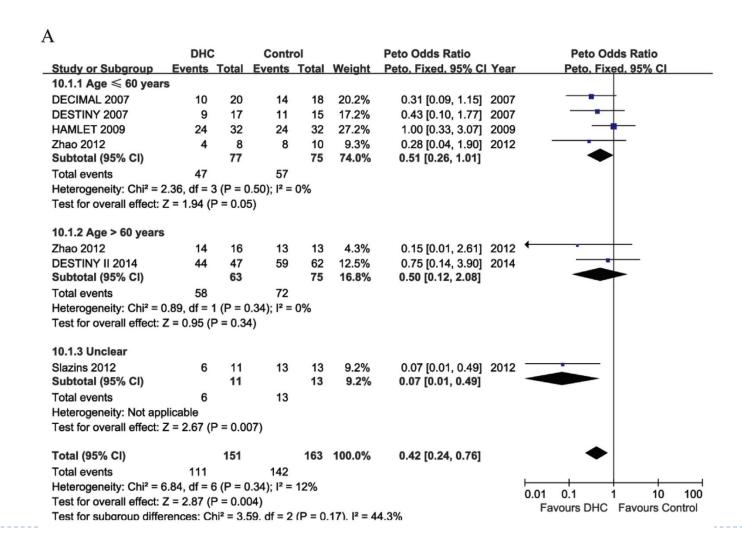
B



Test for subgroup differences: $Chi^2 = 6.46$. df = 2 (P = 0.04). $I^2 = 69.0\%$



Meta-analysis of DH RCTs: Death or Major Disability at 12m (mRS>3)



Would You Want One?

- Survey of healthcare workers in Nsurgery Center in Australia (n=773)
 - ▶ 53% initially would give consent for themselves
 - ▶ 18.1% unwilling to have procedure
 - Only 8.7% felt mRS≥4 was acceptable
 - ▶ 7.4% felt mRS=4 was acceptable
- After review of Outcomes data for DH
 - > 37.8% unwilling
 - But more were ready to accept
 - □ II.9% felt mRS≥4 was acceptable
 - □ 10.2% felt mRS=4 was acceptable
- So, most felt survival with dependency was unacceptable but many would consent in hope for better outcome



DH in Children

- Literature Review (Shah, et al., 2013)
 - ▶ N=26
 - None had mRS equivalent >4!
 - ?Bias in reporting of good outcomes
 - ▶ Even in presence of herniation, low GCS, multiple vascular territories, longer time to surgery
 - Adult prognostic factors may not apply to children
 - Age, time to surgery, infarct size, size of craniectomy, higher GCS score, just one vascular territory, and present of mydriasis
 - Complications noted: infection



Are we there yet? No, but we are getting there

- ▶ Education of Physicians/Nurses/EMT/High risk patients
- Screening Tools to Screen for what?
- Evidence Based Guidelines need Evidence
- We need Pediatric Performance Measures
- Everybody may need Everything Evaluated
- We need to use Pedi Classification systems
- We need both short and long term outcome measures
- More extensive use of PSOM/RRQ and other measures
- Neuropsychological testing in larger multicenter cohorts



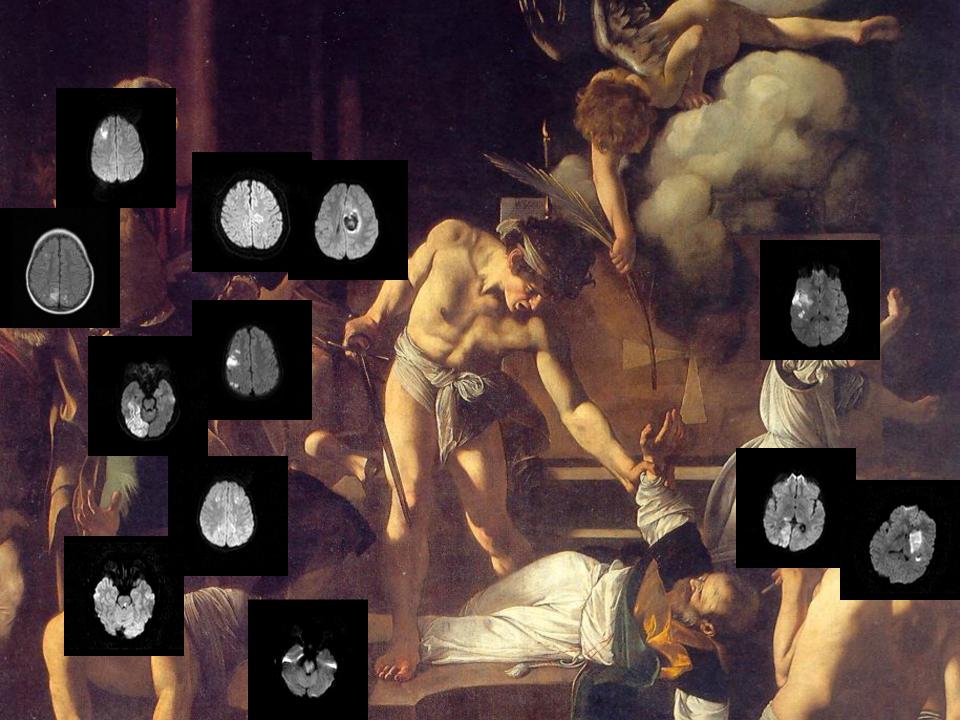
New Model Organism for Adult Stroke Research

- Similar anatomy, neurobiology, and immunology
- NO complicating disease factors
 - Diabetes, HTN, smoking, atherosclerosis
- Superior neuro-regenerative capacity
- Longer lifespan than typical stroke patient
- Willingly participate in rehabilitation programs
- No "Placement issue"
 - Each model organism usually has 2 dedicated therapists/aides









After We Decide What to Measure...Analyzing Outcomes

Dichotomous

- MRS ≥3 is a poor outcome, PSOM ≥1 is a poor outcome
- Dichotomizing outcome scales reduces complexity, but discards substantial outcome information such as improvement...
- Continuous
- ▶ Global Statistic − multiple outcome measures analyzed together
- ▶ Responder Analysis adjusts for baseline severity.
- ▶ **Shift (Rank) Analysis** change in outcome distribution/rank
- ▶ **Rasch Analysis** transforming ordinal scales to interval scales ordinal change of 1 in mRS... mRS $1 \rightarrow 2$ is not the same as $5 \rightarrow 6$

